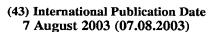
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(54) Title: THERAPEUTIC COMPOSITION FOR TREATMENT OF CANCER BY ARGININE DEPLETION

(57) Abstract: A therapeutic composition and a method for the treatment of cancer by depletion of arginine without systemic complications comprising an arginine decomposing enzyme and protein breakdown inhibitors, a nitric oxide donor, a pressor peptide, and prostacyclin. The composition may further include an amino acid mixture lacking arginine, an antidote for cyanide, blood plasma or its derivatives, and/or a preparation of arginine. The arginine decomposing enzyme may modified to increase circulation half-life and can be type I liver arginase, or type II of human or animal, partially purified, or recombinant, or even bacterial origin. It may be administered as a drug or released from the patient's own tissue. Endogenous production of arginine, particularly via so-called intestinal-kidney axis, can be beneficially inhibited at several enzymatic steps, allowing for deeper reductions of circulating arginine. Different components of the composition may be administered separately, or in suitable mixtures, allowing for needed adjustments during the treatment.





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International application No.

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	INTERNATIONAL SEARCH REPORT	PCT/US03/02342			
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IPC(7) US CL According to In	IFICATION OF SUBJECT MATTER : A61K 38/43, 38/51; G01N 33/53; C12N 15/09, 9/00 : 424/94.1, 94.5; 435/7.71, 69.2, 183, 232 nternational Patent Classification (IPC) or to both national	0, 9/88 classification as	nd IPC		
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CAS STN, W		iata base and, v	here practicable, searc	n terms used)	
- POCT	JMENTS CONSIDERED TO BE RELEVANT		 	Relevant to claim No.	
		priate, of the re	levant passages	1, 4-14, and 17-31	
Category *	Citation of document, with indication, where <u>FF</u> US 6,261,557 (TEPIC et al) 17 July 2001 (17:07.2001),	entire publicati	on.		
Y	Rao et al. Chemopreventive properties of a selective inducible nitric oxide synthase inhibitor in colon carcinogenesis, administered alone or in combination with celecoxib, a selective cyclooxygenase-2 inhibitor. Cancer Res. 2002 Jan 1;62(1):165-70.				
Y A	Rao et al. Chemoprevention of colonic aberrant crypt foci by an inducible nitric oxide synthase-selective inhibitor. Carcinogenesis. 1999 Apr;20(4):641-4. Matthews et al. Nitric oxide-mediated regulation of chemosensitivity in cancer cells. J Natl Cancer Inst. 2001 Dec 19;93(24):1879-85.				
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INTERNATIONAL SEARCH REPORT

international application (vo. PCT/US03/02342

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)					
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:					
Claim Nos.: because they relate to subject matter not required to be searched by this Authority, namely:					
2. Claim Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:					
3. Claim Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).					
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)					
This International Searching Authority found multiple inventions in this international application, as follows: Please See Continuation Sheet					
 As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 					
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 4-14, 17-31					
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.					

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Invention 1 Claim(s) 1, 4-14, and 17-31, drawn to a therapeutic composition comprising an arginine decomposing enzyme and an inhibitor of endogenous production of arginine.

Invention 2 Claim(s) 2 and 4-31, drawn to a therapeutic composition comprising an arginine decomposing enzyme and an inhibitor of intestinal-kideny axis.

Invention 3 Claim(s) 3, 4-14, 17-24, and 26-31, drawn to a therapeutic composition comprising an arginine decomposing enzyme and a nitric oxide donor.

Invention 4 Claim(s) 32 and 33, drawn to a pharmaceutical composition for the reduction of side-effects in cancer therapy.

Invention 5 Claim(s) 34-46, drawn to the use of NO donor for the manufacture of a medicament for the therapy of cancer.

The inventions listed as Inventions 1-4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

No special technical feature exits between Inventions 1-5. Although Inventions 1-5 share a common property of being a therapeutic composition, they do not share a significant structural element since an inhibitor of endogenous production of arginine, an inhibitor of intestinal-kideny axis, and a nitric oxide donor are different chemical entities with different structural features. Furthermore, a therapeutic composition comprising arginine decarboxylase, which is an arginine decomposing enzyme, has already been taught in the prior art by US 6,261,557, wherein the said therapeutic composition comprising arginine decarboxylase is used for the treatment of cancer(see entire publication).